Phytochemistry, Vol. 23, No 9, pp 1855–1863, 1984.
Printed in Great Britain

0031-9422/84 $3.00+0.00

A MATHEMATICAL ADDITIVE MODEL OF THE STRUCTURE–ACTIVITY RELATIONSHIPS OF GIBBERELLINS*

EDWARD P. SEREBRYAKOV,†§ NAUM A. EPSTEIN,‡ NATALYA P. YASINSKAYA‡ and ANATOLY B. KAPLUN‡

†N.D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, 117913 Moscow, Leninsky Prospect 47, U.S.S.R.; ‡Institute for Biological Testing of Chemical Compounds, Kupavna, Moscow Region, U.S.S.R.

(*Received* 30 *August* 1983)

Key Word Index—*Pisum sativum*; Leguminosae; dwarf pea; *Cucumis sativus*; Cucurbitaceae; cucumber; *Lactuca sativa*; Compositae; lettuce; Free–Wilson approach; gibberellins; potency in bioassays; substituent contributions.

Abstract—By means of a modified Free–Wilson technique, the individual contributions of 22 different substituents on the growth-promoting activity of 67 gibberellins and their synthetic derivatives were estimated for three bioassay systems (dwarf pea, cucumber and lettuce). Statistically significant correlations between the presence of certain structural elements and potency in a given bioassay were observed. The additive character of the contributions is considered in terms of a structural correspondence between a C_{19}-hormone and a specific receptor.

INTRODUCTION

The structure–activity relationship of the gibberellins has received much attention ([1] and references cited therein) but has been considered only in a qualitative manner. The great variability in the position of functional groups coupled with a limited choice of substituents in any given position (e.g. at C-3) make gibberellins unsuitable for the description of the structure–activity relationship by the Hansch approach, where the activity is directly correlated with the physical parameters of the molecule [2]. An alternative approach, developed by Free and Wilson and based on the principle of additivity of the contribution made by substituents to the physiological activity of a molecule [3], appears to be more promising for such complex chemicals as gibberellins.

In this communication, we show the possibility of using a mathematical, additive model of the Free–Wilson type as a means for a semiquantitative evaluation of the growth-promoting potencies of gibberellins and their acidic, non-conjugated derivatives in three standard bioassay systems which employ intact seedlings of dwarf pea (*Pisum sativum*), cucumber (*Cucumis sativus*) and lettuce (*Lactuca sativa*), respectively.

EVALUATION AND MANIPULATION OF DATA

A uniform presentation of the experimentally found growth-promoting potencies has been secured by means of a five-point scale, the principle and the use of which were described in our previous communication [1]. Data expressed by use of other scales [4, 5] were thus adapted in a form suitable for mathematical treatment. The scale used in this work approximates the decimal logarithmic scale: compounds with maximal potency in a given bioassay are rated as 4, compounds displaying potency within 10 to *ca* 99% of the maximum are rated as 3, those with potency within 1–9% of the maximum as 2, weakly active compounds with potency *ca* 0.1–0.9% of the maximum as 1, and those with a potency below this level are given a zero (0) potency index.

The problem of assessing these relative potency indices to compounds tested by different authors under non-identical conditions was solved, whenever possible, by comparison of the dose–response curves based on original data [5–10]. When potency indices could not be assessed unambiguously because of an irregular shape of the dose–response curves, the response induced by doses ranging from 1×10^{-2} to 10^{0} μg per plant were considered the most reliable. If the original data from different sources were not in conformity (e.g. in the case of GA_9 and GA_{20} in the dwarf pea test), the potency index was taken either as the nearest to the average from three and more results or as given in refs. [1] and [4], if only two possibilities were open for choice.

In order to evaluate the contributions to the physiological activity made by different substituents, the latter were presented as attached to the molecular framework of gibberellins shown in Fig. 1. Structural elements supplementary to this framework were the groups A, B, C, D, E, F, G and A′, representing altogether 22 different substituents. When positions C and D were occupied simultaneously by two *cis*-oriented (2β, 3β) hydroxyl groups a correction factor (H^*) was introduced to account for their interaction.

Activity contributions from the molecular framework (μ) and from the fragments shown in Fig. 1 were obtained by means of regressional analysis, i.e. by solving, with the use of the least-squares method, N simultaneous linear equations which correlate the growth-promoting potency of the jth compound (A_j) with the presence of a given structural element whose activity contribution (a_k) is assumed to be independent and additive:

$$A_j = \mu + a_1x_1 + a_2x_2 + \ldots + a_kx_k \qquad (1)$$

*Part 2 in the series "Structure–Activity Study of Gibberellins". For Part 1 see ref. [1].

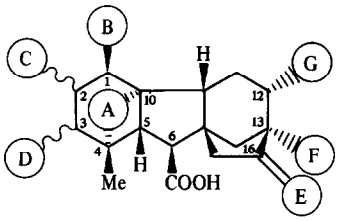
§To whom correspondence should be addressed.

Table 1. The matrix for the system of equations of type (1) and the growth-stimulating activity indices (A_j) in the three plant bioassays (the structures of GA_1–GA_{51} and of compounds **1–32** are given in Figure 2)

GA_s	j ($1 \rightarrow N$)	A			B		C			D				E					F		G	A′		H^*	Dwarf pea, A_j		Cucumber, A_j		Lettuce, A_j	
		x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}	x_{11}	x_{12}	x_{13}	x_{14}	x_{15}	x_{16}	x_{17}	x_{18}	x_{19}	x_{20}	x_{21}	x_{22}	x_{23}	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
GA_1	1	1			1						1			1					1						3	3.27	2	1.66	3	2.34
GA_2	2	1									1					1	1								2	1.82	2	2.29	2	1.25
GA_3	3	1									1			1					1						4	3.39	2	1.79	3	3.04
GA_4	4	1									1			1											3	3.22	3	3.69	2	2.69
GA_5	5	1							1					1					1						3	2.86	1	0.29	2	1.99
GA_7	6	1			1						1			1											3	3.34	4	3.82	4	3.39
GA_9	7	1												1											2	1.59	3	3.11	3	2.20
GA_{10}	8	1														1	1								0	0.19	2	1.71	0	0.76
GA_{12}	9													1								1			0	0.15	1	1.01	0	0.12
GA_{13}	10										1			1									1		0	2.01	0	2.02	1	0.93
GA_{14}	11										1			1								1			0	1.78	0	1.81	0	0.61
GA_{15}	12		1											1											1	1.02	2	2.39	2	1.53
GA_{17}	13													1					1			1			0	0.20	0	0.80	0	−0.23
GA_{18}	14										1			1					1			1			2	1.83	0	0.62	1	0.26
GA_{19}	15			1										1					1						0	0.46	0	0.20	1	0.33
GA_{20}	16	1												1					1						1	1.64	0	1.08	3	1.85
GA_{23}	17			1							1			1					1						2	2.09	0	0.78	1	0.82
GA_{24}	18			1										1											1	0.41	3	2.23	0	0.68
GA_{25}	19													1									1		0	0.38	1	1.44	0	0.44
GA_{28}	20										1			1					1				1		0	2.06	0	−0.01	0	0.58
GA_{29}	21	1						1						1					1						0	0.43	0	−0.17	0	0.35
GA_{30}	22	1			1						1			1							1				3	2.89	1	1.36	1	1.43
GA_{31}	23	1							1					1							1				2	2.36	0	−0.14	0	0.38
GA_{33}	24	1				1							1	1							1				1	0.75	0	−0.21	1	0.20
GA_{36}	25			1							1			1											2	2.04	3	2.81	1	1.17
GA_{37}	26		1								1			1											2	2.65	3	2.97	2	2.02
GA_{38}	27		1								1			1					1						3	2.72	1	0.94	0	1.67
GA_{40}	28	1					1							1											0	0.18	2	1.71	1	0.76
GA_{46}	29							1						1									1		0	−0.83	0	0.19	0	−1.06
GA_{47}	30	1					1				1			1											2	1.81	2	2.29	1	1.25
GA_{51}	31	1						1						1											0	0.38	0	1.86	0	0.70

1	32	1							1					1											3	2.81	2	2.32	—	—
2	33	1			1							1		1					1						2	1.89	1	0.95	1	0.26
3	34	1			1						1			1						1					3	2.74	3	2.92	3	3.28
4	35	1			1							1		1						1					1	1.24	3	2.08	2	1.70
5	36	1			1							1		1											2	1.84	3	2.98	2	1.81
6	37	1			1					1				1					1						2	1.34	1	0.57	2	1.47
7	38	1								1				1					1						1	1.22	0	0.44	0	0.77
8	39	1								1				1											1	1.17	3	2.47	1	1.12
9	40		1							1				1											1	0.60	2	1.75	0	0.45
10*	41	1								1						1			1						0	0.35	0	0.22	0	0.48
11*	42	1								1								1	1						2	1.31	0	0.62	1	0.67
12	43	1				1							1	1					1						1	1.25	0	0.22	1	1.81
13	44	1											1	1					1						3	2.53	0	0.66	1	1.32
14	45	1											1	1											3	2.48	3	2.69	2	1.67
15	46	1			1								1	1					1						2	2.65	0	0.79	2	2.02
16	47	1			1								1	1											2	2.60	3	2.82	1	2.37
17*	48	1											1			1			1						2	1.66	0	0.44	0	0.07
18*	49	1											1					1	1						3	2.62	2	0.84	1	1.22
19	50	1									1				1				1						2	1.90	1	0.85	1	1.20
20	51	1									1				1										2	1.85	3	2.88	2	1.55
21	52	1													1										0	0.22	2	2.30	1	1.06
22	53	1			1						1				1				1						2	2.02	1	0.98	1	1.90
23*	54	1									1					1			1						3	2.40	1	1.44	2	1.09
24*	55	1									1							1	1						3	3.36	2	1.84	2	2.24
25*	56	1														1			1						2	0.77	0	0.86	1	0.60
26*	57	1																1	1						2	1.73	0	1.26	2	1.75
27*	58	1							1							1			1						2	1.99	0	0.07	1	0.74
28*	59	1							1									1	1						3	2.95	0	0.47	2	1.89
29	60	1																							2	2.00	3	3.00	1	1.00
GA_8	61	1						1			1			1					1					1	1	0.87	0	−1.15	0	−0.86
GA_{27}	62		1					1			1			1										1	1	0.25	0	0.16	0	0.32
GA_{34}	63	1						1			1			1										1	1	0.82	0	0.88	0	0.99
GA_{43}	64							1			1			1									1	1	0	−0.39	0	−0.79	0	−0.77
30*	65	1						1			1								1					1	0	0.75	0	0.38	0	−2.11
31*	66	1						1			1							1						1	2	0.91	0	0.59	0	−0.61
32*	67																	1	1						0	−0.45	0	0.22	0	0.27
No. of examples		48	5	4	11	2	2	9	5	6	27	3	8	47	4	8	2	7	32	2	3	4	5	6						

*Stereochemistry at C-16 in compounds **10**, **11**, **17**, **18**, **23–28**, **31** and **32** (all tested by Brian *et al.* [4]) is assigned on the basis of NMR data [14].



Framework: k_0
Group A: k_1(–COO–, γ-lactone); k_2(–$COOCH_2$–, δ-lactone); k_3(–COOCHOH, δ-lactol)
Group B. k_4 (Δ^1-double bond); k_5(1β-OH)
Group C: k_6(2α-OH); k_7(2β-OH); k_8(Δ^2-double bond)
Group D: k_9(3α-OH); k_{10}(3β-OH); k_{11}(3β-OMe); k_{12}(3-oxo)
Group E: k_{13}(=CH_2, Δ^{16}-double bond); k_{14}(16-oxo, 17-nor); k_{15}(16β-Me); k_{16}(16α-OH); k_{17}(16α-Me, '16-epi-series')
Group F: k_{18}(13α-OH); k_{19}(13α-OMe)
Group G. k_{20}(12α-OH)
Group A' ('open group A'). k_{21}(10α-Me, 4α-COOH); k_{22}(10α-COOH, 4α-COOH)
Correction factor H^*(2β-OH. 3β-OH interaction). k_{23}

Fig. 1. The gibberellin framework and the groups of substituents.

where A_j is the experimentally found growth-promoting potency index of the jth compound expressed by means of the quasi-logarithmic five-point scale; x_k is the fictitious variable equal to 1 if the jth compound contains the kth fragment, or to 0 if this fragment is absent; $j = 1, 2, 3 \ldots N$ is the ordinal number of a given compound (and the number of the corresponding equation); and $k = 0, 1, 2, 3 \ldots$ is the number of substituents including also the framework as a special substituent whose contribution ($\mu = a_0 x_0$ when $x_0 = 1$) is assumed to be a constant.

For the computerized solution the system of equations was re-written in a matrix form, presented in Table 1. In contrast to the original Free–Wilson technique [3], the restriction equations were not used. The activity contributions of H atoms at each position were set to zero so that the activity contribution of a substituent is relative to that of H (cf. [11, 12]). For the calculation of μ and a_k, the least sum of squares of deviations between the calculated values of A_j and the corresponding experimentally found potency indices was taken as a criterion. In the calculations of μ and a_k for each of the three bioassays the equations giving $|A_{j(\text{calc})} - A_{j(\text{exp})}| \geqslant 1$ (not more than four such equations for a bioassay) were discarded. This trial enabled us to minimize the deviations both for the whole system of equations and for the majority of individual equations, particularly for the compounds with potency indices 4 and 3. Hence, the value $|A_{j(\text{calc})} - A_{j(\text{exp})}|$ served as a criterion for the correctness of adaptation of experimental data.

Statistical parameters characterizing the solution of the system of equations for each bioassay were calculated as recommended for the Free–Wilson method [13]:
Coefficient of multiple correlation

$$R = \sqrt{m^2/l^2} \tag{2}$$

Fisher's criterion

$$F_{(k-1,N-1)} = m^2(N-k)/d^2(k-1) \tag{3}$$

Explained variance

$$EV = 1 - d^2(N-1)/l^2(N-k) \tag{4}$$

where

$$m^2 = \sum_1^N [A_{j(\text{calc})} - \overline{A}_{j(\text{exp})}]^2$$

$$l^2 = \sum_1^N [A_{j(\text{exp})} - \overline{A}_{j(\text{exp})}]^2$$

$$d^2 = \sum_1^N [A_{j(\text{exp})} - A_{j(\text{calc})}]^2$$

In order to check the conditionality of the matrices of Table 1, the calculations of μ, a_k, R, F and EV were carried out with the potency indices altered by $\pm 5\%$ for each compound. The values μ and a_k thus obtained differed from those found in the main variant by *ca* 5%, while the parameters R, F and EV remained constant with an accuracy of ± 0.0010.

The compounds and hence the equations presented in Fig. 1 and Table 1 ($N = 67$, see accompanying formulae) were selected in such a way that each structural element could be found at least twice. For this reason gibberellins with unique structural features (GA_6, GA_{11}, GA_{21}, GA_{22}, GA_{26}, GA_{32}, GA_{35}) were not included in the system of equations. On the other hand, in order to avoid the singularity of the system and to secure the linear independence of variables, two equations representing two structurally unique compounds (**29** and **32**, lines 60 and 67 in the matrix of Table 1) were included.

All calculations were performed on an EC-1030 computer with the program written in Fourtran-IV.

The calculated values of μ and a_k in the three bioassays, as well as the statistical parameters R, F and EV for each bioassay, are given in Table 2. The values of $A_{j(\text{calc})}$, obtained from eqn. (1) as the sum of activity contributions, and the corresponding values of $A_{j(\text{exp})}$ found for gibberellins and their synthetic derivatives are given in the right hand part of Table 1.

RESULTS AND DISCUSSION

The set of compounds presented in Fig. 2 and Table 1 ($N = 67$) contains in various combinations 22 structural elements occurring in gibberellins and their derivatives. This set comprises 35 natural gibberellins and 32 of their close semi-synthetic analogues (**1–32**).

Since this set satisfies the condition:

$$N \geqslant 1 + (A-1) + (B-1) + (C-1) + (D-1) + (E-1) + (F-1) + (G-1) + (A'-1) + (H^*-1) \tag{5}$$

where A, B, C, etc. = the total number of substituents at each position (see Fig. 1), the application of the Free–Wilson method is justified (see ref. [3]). As follows from the comparison of $A_{j(\text{calc})}$ and $A_{j(\text{exp})}$ for each bioassay (Table 1) and from the statistical parameters (Table 2), the correlation between the calculated and the experimentally found potency indices is good for the dwarf pea and the cucumber bioassays ($R > 0.90$) and satisfactory for the lettuce test ($R > 0.85$). This result obtained with a rather large number of compounds containing many structural elements in variety of combinations shows that *in the majority of cases the activity contributions from each element are independent and additive.*

Table 2. Mathematical activity contributions from the molecular framework (μ) and the substituents (a_k) in the growth-stimulating potency of gibberellins and their derivatives in three bioassays

Contributions and contributing groups	Bioassay		
	Dwarf pea	Cucumber	Lettuce
μ (molecular framework)	−0.18	1.96	−0.48
a_1 (–COO–, γ-lactone)	2.18	1.04	1.48
a_2 (–$COOCH_2$–, δ-lactone)	1.61	0.32	0.81*
a_3 (–COOCHOH, δ-lactol)	1.00	0.16	−0.04
a_4 (Δ^1-double bond)	0 12	0.13	0.70
a_5 (1β-OH)	−1.28	−0.44	0.49
a_6 (2α-OH)	−1.41	−1.40	−1.44
a_7 (2β-OH)	−1.21	−1.25	−1.50
a_8 (Δ^2-double bond)	1.22	−0.79	0.14
a_9 (3α-OH)	−0.42	−0.64	−1.08
a_{10} (3β-OH)	1.63	0.58	0.49
a_{11} (3β-OMe)	0.13	−0.26	−1 09
a_{12} (3-oxo)	0.89	−0 42	−0.53
a_{13} (=CH_2, Δ^{16}-double bond)	−0.41	0 11	1 20
a_{14} (16-oxo, 17-nor)	−1.78	−0.70	0.06
a_{15} (16β-Me)	−1 28	−0 11	0.05
a_{16} (16α-OH)	−0.53	−1.18	−0.19
a_{17} (16α-Me, '16-epi-series')	−0.32	0.29	1 10
a_{18} (13α-OH)	0.05	−2.03	−0.35
a_{19} (13α-OMe)	−0.60	−0.90	−0.11
a_{20} (12α-OH)	−0.45	−2.46	−1.96
a_{21} (10α-Me, 4α-COOH)	0.74*	−0.84	−0.60
a_{22} 10α-COOH, 4α-COOH)	0 97*	−0.63*	−0.28
a^*_{23} (2β-OH: 3β-OH)	−1 19	−1.56	−1.70
Statistical parameters			
R	0.9324	0 9199	0.8764
$F(k-1,N-k)$	11.301	9.332	5.620
EV	0.7925	0.7555	0.6315
Excluded equations (j in Table 1)	10, 11, 20	10, 11, 16, 31	27, 47

*These contributions are altered by up to ± 0.50 if the excluded equations are taken into account

Although the starting $A_{j(\exp)}$ indices were assessed only as orders of magnitude, there exists a qualitative agreement between the $A_{j(\text{calc})}$ and the actual experimental data. Thus, the $A_{j(\text{calc})}$ values of the eight most studied C_{19}-gibberellins in the dwarf pea test are compatible with the experimentally observed hierarchy of these gibberellins at the levels 1×10^{-2} and 1×10^{-1} μg per plant.

The calculated potency indices are: GA_3 (3.39) $\geqslant GA_7$ (3.34) $\geqslant GA_1$ (3.27) $\geqslant GA_4$ (3.22) > GA_5 (2.86) > GA_{20} (1.64) $\geqslant GA_9$ (1.59) > GA_8 (0.87).

The length of the dwarf pea epicotyl (in mm) at 1×10^{-1} μg of GA_x per seedling [5]: GA_3 (218.1) > GA_7 (196.2) > GA_1 (149.7) > GA_4 (123.4) $\geqslant GA_5$ (122.7) > GA_{20} (68.5) = GA_9 (68.5) > GA_8 (61.4) > water (57.8).

At the levels 1×10^0 and 1×10^1 μg per plant, GA_4 is significantly more active than GA_5 [5, 7] while GA_{20} is either somewhat less active [5] or somewhat more active than GA_9 [10].

Among the activity contributions made by different substituents (see Table 2), some are invariably growth-stimulating (γ-lactone, 3β-OH, δ-lactone, Δ^1-double bond) or growth-reducing (2α-OH, 2β-OH, 12α-OH) while the rest vary with the type of bioassay. It would be reasonable to classify the a_k values of Table 2 as strong ($|a_k| \geqslant 0.50$), significant ($|a_k| \geqslant 0.10$) and insignificant ($|a_k| \leqslant 0.10$) since such a classification would emphasize the increasing unreliability of mathematical determination of activity contributions of small absolute value.

The calculations of potency indices for gibberellins containing the 2β,3β-diol group (GA_8, GA_{27}, GA_{34}) gives excessive values when a correction factor for the specific interaction of two hydroxyls (a^*_{23}) is not taken into account. The deviation from the additivity in all three bioassays implies that the 2β,3β-diol group brings about a specific growth-inhibiting effect and from this point of view should be considered a particular structural element. In order to estimate the activity contribution of this element, another system of 67 equations, analogous to that presented in Table 1, was solved by the least-squares method. In this case, the contribution of the 2β,3β-diol group (a'_{23}) was taken as an independent value and in equations corresponding to the compounds with this group present, the separate contributions from 2β-OH and 3β-OH were omitted. Both variants of calculations gave practically the same values of all activity contri-

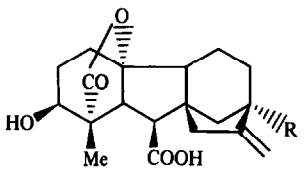
butions. It was thus found that:

$$a'_{2\beta\text{-OH},\,3\beta\text{-OH}} \approx a_{2\beta\text{-OH}} + a_{3\beta\text{-OH}} + a^{*}_{2\beta\text{-OH}\ 3\beta\text{-OH}} \quad (6)$$

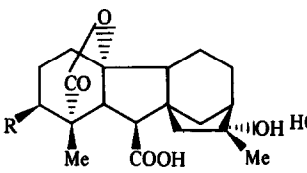
where $a'_{2\beta\text{-OH},3\beta\text{-OH}}$ is the activity contribution of the $2\beta,3\beta$-diol group (a'_{23} in the second variant of calculations); $a_{2\beta\text{-OH}}$ and $a_{3\beta\text{-OH}}$ are the two separate contributions of hydroxyls (a_7 and a_{10} in the main variant of calculations); and $a^{*}_{2\beta\text{-OH}\ 3\beta\text{-OH}}$ is the correction factor accounting for the interaction of these hydroxyls (a^{*}_{23} in the main variant).

The somewhat low $A_{j(\mathrm{calc})}$ values of the two most potent gibberellins (GA_3 and GA_7) in the dwarf pea and in the lettuce bioassays may be due to the fact that the activity contribution of the Δ^1-double bond in GA_3 and GA_7 was assumed to be the same as in the corresponding α,β-enones, **15** and **16**. Chemically speaking, this assumption cannot be true. Characteristically, these enones tend to

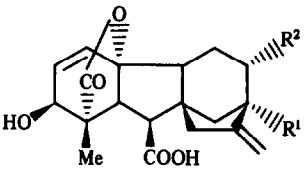
C_{19}– Gibberellins and their Derivatives



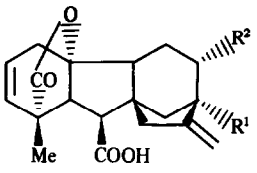
GA_1 R = OH
GA_4 R = H



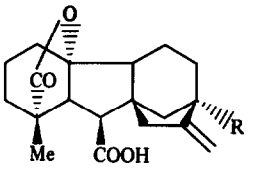
GA_2 R = OH
GA_{10} R = H



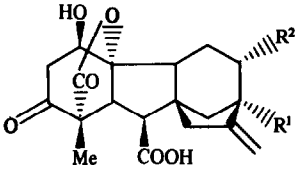
GA_3 R^1 = OH, R^2 = H
GA_7 R^1 = R^2 = H
GA_{30} R^1 = H, R^2 = OH



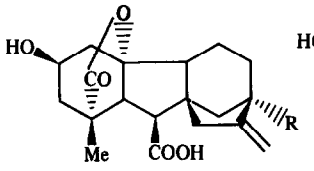
GA_5 R^1 = OH, R^2 = H
GA_{31} R^1 = H, R^2 = OH
1 R^1 = R^2 = H



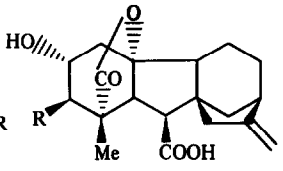
GA_9 R = H
GA_{20} R = OH



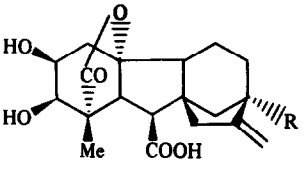
GA_{33} R^1 = H, R^2 = OH
12 R^1 = OH, R^2 = H



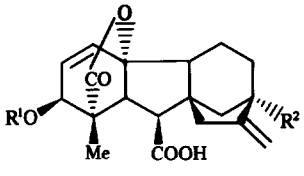
GA_{29} R = OH
GA_{51} R = H



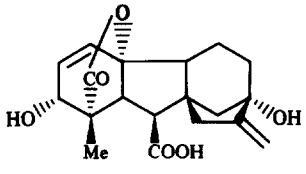
GA_{40} R = H
GA_{47} R = OH



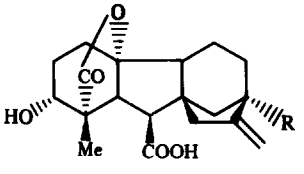
GA_8 R = OH
GA_{34} R = H



2 R^1 = Me, R^2 = OH
3 R^1 = H, R^2 = OMe
4 R^1 = Me, R^2 = OMe
5 R^1 = Me, R^2 = H



6



7 R = OH
8 R = H

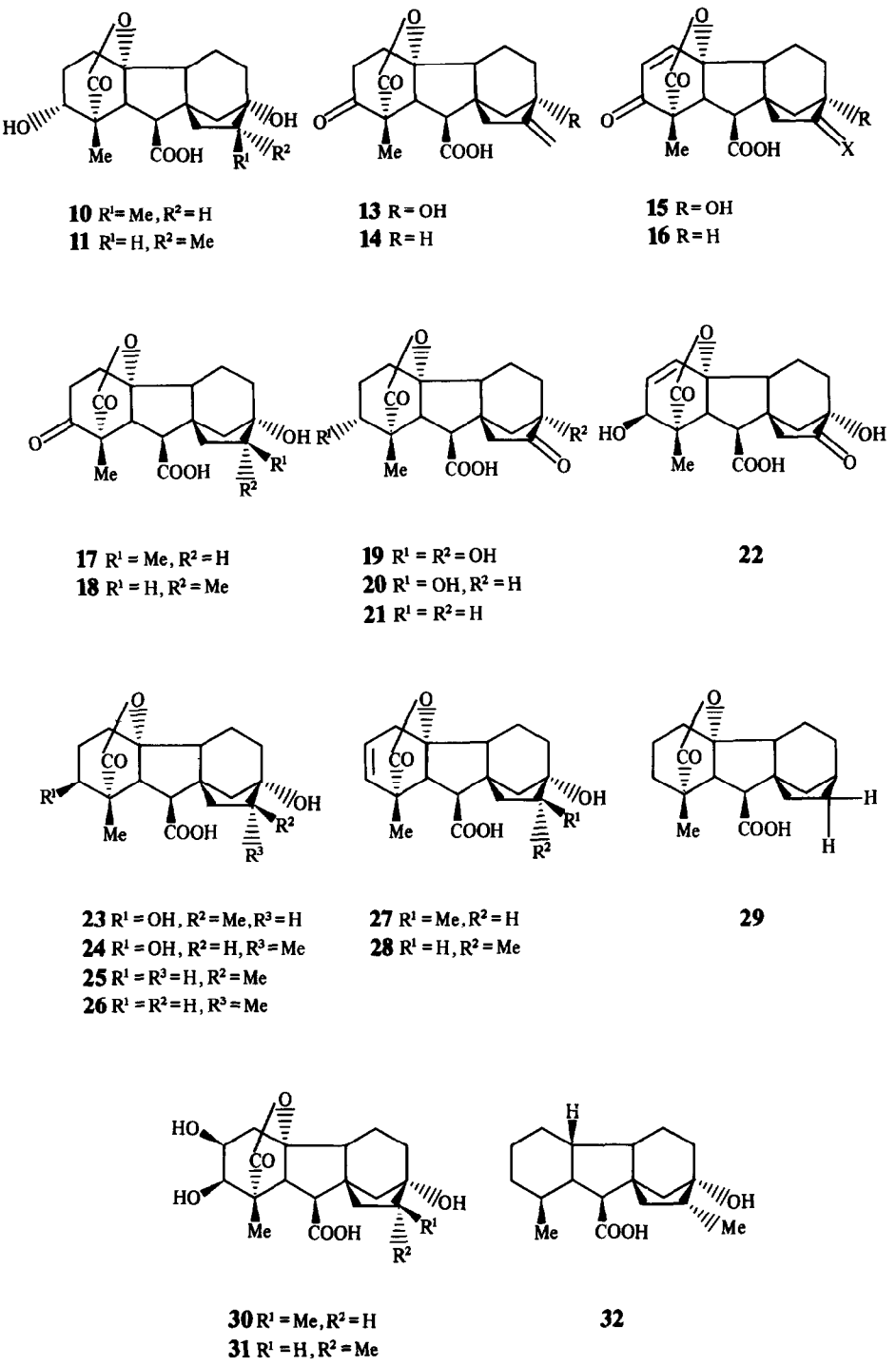
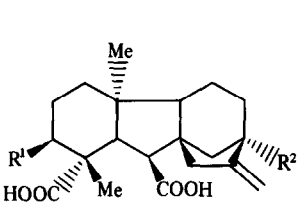


Fig. 2. Structures of gibberellins.

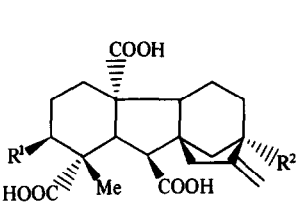
give excessive $A_{j(calc)}$ values which imply the necessity to consider the α,β-enone group as a separate structural element or introduce a correction factor for it.

Our present knowledge of the general trend of the biosynthesis of C_{19}-gibberellins in plants [15] indicates that their early precursors are the C_{20}-gibberellins with a methyl group at C-10 (such as GA_{12}, GA_{14}, GA_{18} and the like) while the C_{20}-gibberellins with a carboxyl group at this position (such as GA_{25}, GA_{13}, GA_{46}, GA_{28} and the like) appear to deviate from the main pathway of biosynthesis. The nearest so far known precursors of C_{19}-gibberellins among their C_{20}-congeners are aldehydic acids (δ-lactols) such as GA_{24}, GA_{36}, GA_{19} and GA_{23}. The corresponding δ-lactones (GA_{15}, GA_{37}, GA_{38} and the like) seem to represent a metabolic 'blind alley' diverted from the main pathway, and therefore they are

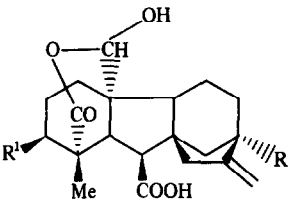
C_{20} Gibberellins



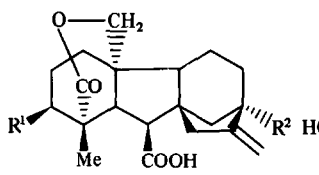
GA_{12} $R^1 = R^2 = H$
GA_{14} $R^1 = OH, R^2 = H$
GA_{17} $R^1 = H, R^2 = OH$
GA_{18} $R^1 = R^2 = OH$



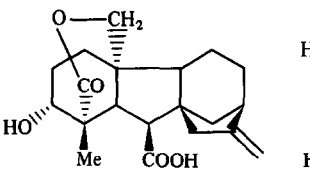
GA_{13} $R^1 = OH, R^2 = H$
GA_{25} $R^1 = R^2 = H$
GA_{28} $R^1 = R^2 = OH$



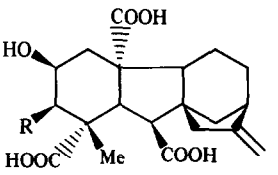
GA_{19} $R^1 = H, R^2 = OH$
GA_{23} $R^1 = R^2 = OH$
GA_{24} $R^1 = R^2 = H$
GA_{36} $R^1 = OH, R^2 = H$



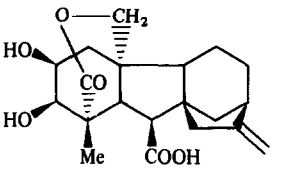
GA_{15} $R^1 = R^2 = H$
GA_{37} $R^1 = OH, R^2 = H$
GA_{38} $R^1 = R^2 = OH$



9



GA_{43} R = OH
GA_{46} R = H



GA_{27}

unlikely to be precursors of the C_{19}-gibberellins. From this point of view, it is noteworthy that in all three bioassays the activity contributions can be ranged in nearly the same order:

$$\gamma\text{-lactone} > \delta\text{-lactone} > \delta\text{-lactol} \gtrless 10\alpha\text{-COOH}, 4\alpha\text{-COOH} \gtrless 10\alpha\text{-Me}, 4\alpha\text{-COOH}$$
$$(a_1) \qquad (a_2) \qquad (a_3) \qquad (a_{22}) \qquad (a_{21})$$

This tendency is compatible with the assumption that in the dwarf pea, cucumber and lettuce bioassays the physiological response is determined mainly by the topological correspondence between a C_{19}-hormone molecule and the 'recognition site' of a specific receptor [1]. For an efficient hormone–receptor contact to occur, the presence of the γ-lactone group is required: the less another structural element can mimic it, the weaker the response. The influence of the metabolic factor is probably reflected in the higher rate of incorrect $A_{j(\text{calc})}$ values for C_{20}-gibberellins. The additivity of activity contributions from as many as 22 different substituents speaks in favour of the prime importance of the hormone–receptor contact for the development of physiological response.

REFERENCES

1. Serebryakov, E. P., Agnistikova, V N. and Suslova, L M. (1984) *Phytochemistry* **23**, 1847.
2. Fujita, T (1972) in *Biological Correlations—the Hansch Approach.* Adv. Chem. Ser, Vol. 114, p. 1.
3. Craig, P N. (1972) in *Biological Correlations—the Hansch Approach.* Adv Chem Ser., Vol. 114, p. 115
4. Brian, P. W., Growe, J. F and Mulholland, T. P. C. (1967) *Phytochemistry* **6**, 1475.
5. Crozier, A., Kuo, C. C., Durley, R. C and Pharis, R. P. (1970) *Can J Botany* **48**, 867.
6. Yokota, T., Murofushi, N., Takahashi, N. and Katsumi, M. (1971) *Phytochemistry* **10**, 2943.
7. Yamane, H., Yamaguchi, H., Yokota, T, Murofushi, N., Takahashi, N. and Katsumi, M. (1973) *Phytochemistry* **12**, 255.
8. Reeve, A. and Crozier, A (1975) in *Gibberellins and Plant Growth* (Krishnamoorthy, H. N., ed.), p. 35. Wiley Eastern, New Delhi
9. Hoad, G V., Pharis, R. P, Railton, I. D. and Durley, R. C. (1976) *Planta* **130**, 113
10. Sponsel, V M, Hoad, G V and Beely, L J (1977) *Planta* **135**, 143.
11. Cammarata, A. and Suh Jen Yan (1970) *J Med Chem* **13**, 93

12. Fujita, T. and Ban, T (1971) *J. Med. Chem.* **14**, 148.
13. Hudson, D. R., Bass, G. E. and Purcell, W. P. (1970) *J. Med. Chem.* **13**, 1184.
14. Mori, K. (1972) *Agric. Biol. Chem.* **36**, 2519.
15. Graebe, J. E. and Ropers, H. J. (1978) in *Phytohormones and Related Compounds: a Comprehensive Treatise* (Letham, D. S., Goodwin, P. B. and Higgins, T. J. V., eds.), Vol. 1, p. 107. Elsevier–North-Holland, Amsterdam.